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Fluoroalkylative Aryl Migration of Conjugated *N*-Arylsulfonylated Amides Using Easily Accessible Sodium Di- and Monofluoroalkanesulfinates

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Supporting Information

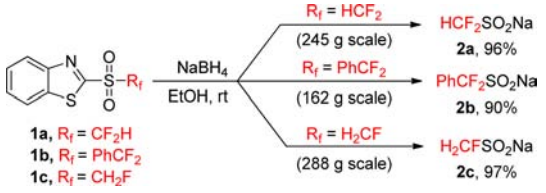
ABSTRACT: Fluorinated sulfinate salts R_fSO_2Na (R_f = CF_2H, CF_2Ph, and CH_2F) have been prepared via $NaBH_4$-mediated reduction of the corresponding benzo[*d*]thiazol-2-yl sulfones, and their synthetic application as di- and monofluoroalkyl radical precursors is demonstrated in the silver-catalyzed cascade fluoroalkylation/aryl migration/SO_2 extrusion of conjugated *N*-arylsulfonylated amides.

Molecules containing fluorine atoms have been widely applied in modern pharmaceuticals, agrochemicals, and materials.[1,2] For instance, the selective incorporation of a fluoroalkyl group into drugs or bioactive molecules often significantly alters their metabolic stability, lipophilicity, and biopotency.[1,3] Hence, it has been of great synthetic interest to develop new, efficient methods for incorporating fluoroalkyl group(s) into organic molecules. Methods for the incorporation of the CF_3 group into organic molecules have been extensively studied,[4] among which the radical trifluoromethylation of various substrates has attracted much attention recently due to the mildness of the reaction conditions.[5] However, methods for the straightforward introduction of CF_2H and CH_2F groups via a radical process are limited.[6]

Recently, elegant work from the Baran group described direct C−H di- and monofluoromethylation of heteroarenes using zinc sulfinate salts as fluoroalkyl radical sources.[7] However, in contrast to the readily available sodium trifluoromethanesulfinate, complex procedures for the preparation and purification of the zinc sulfinates may hamper their broad application as practical di- and monofluoromethylation reagents.[8] On the other hand, Chen and co-workers reported the preparation of sodium difluoromethanesulfinate using difluoromethyl halides, but the yield was low and the purification was difficult.[9] Prakash and co-workers also reported that the fluorinated sodium sulfinates could be prepared from a reaction between difluoroalkyl 2-pyridyl sulfone and EtSNa, but the use of smelly ethanethiol (EtSH) is less preferred.[10] Therefore, a simple, efficient, and environmentally friendly method for the preparation of fluorinated sulfinate salts is highly desired. In this paper, we disclose our recent success in developing a concise preparation of sodium sulfinates R_fSO_2Na (R_f = CF_2H, CF_2Ph, and CH_2F), examining their synthetic utility in radical fluoroalkylation of alkenes, and making a comparison on the reactivity of these R_fSO_2Na reagents.

In this research, we found that difluoromethyl benzo[*d*]-thiazol-2-yl (BT) sulfone (**1a**), which is readily available from 2-mercaptobenzothiazole,[10,11] can be readily converted to HCF_2SO_2Na in high yield after a modification of Ueno's procedure for preparing nonfluorinated sulfinate salts.[12] Thus, the treatment of an ethanol solution of sulfone **1a** with a slight excess of $NaBH_4$, followed by precipitation of the resulting salt in hexanes and washing with ethanol/hexanes, afforded HCF_2SO_2Na (**2a**) in 96% yield (Scheme 1). Similarly, other sodium sulfinates $PhCF_2SO_2Na$ (**2b**) and H_2CFSO_2Na (**2c**) were obtained from the corresponding BT sulfones[13,14] in 90%

Scheme 1. Preparation of Sodium Di- and Monofluoroalkanesufinates



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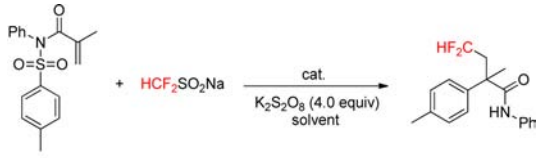
and 97% yields, respectively (Scheme 1). These sodium sulfinate salts are stable white solids, and their high purity was confirmed by elemental analysis (see the Supporting Information). Note that the preparation and purification procedures are very simple, thus providing an efficient pathway for rapid, large-scale preparation of these fluorinated sulfinate salts.

With these easily accessible reagents in hand, we set out to test their synthetic utility. Nevado et al. reported a radical trifluoromethylation/aryl migration/SO_2 extrusion of *N*-arylsulfonylated amides with Togni's reagent.[15,16] They found that the reaction of *N*-arylamides affords α-aryl-β-trifluoromethyl amides, while the reaction of *N*-alkylamides gives trifluoromethylated oxindoles resulting from a further cyclization via the C(sp^2)−N bond formation. Inspired by their work, we investigated the radical di- and monofluoroalkylation of conjugated *N*-arylsulfonylated amides with our sodium sulfinates to compare the reaction features of these radical sources.

At the outset, we chose the reaction between reagent **2a** and *N*-tosylamide **3a** as a model reaction to survey the reaction conditions. As shown in Table 1 (for details, see Tables S1−S7 in the Supporting Information), a screening of solvents demonstrated that DMSO was the best solvent. When $AgNO_3$ was used as a catalyst, the desired product **4a**, which was formed via a series of transformations including difluoromethylation, intramolecular 1,4-aryl migration, desulfonylation, and H atom abstraction, was obtained in 62% yield (Table 1, entry 3). A screening of silver catalysts showed that $AgNO_3$ exhibited higher activity (Table 1, entries 3 and 5−7). Furthermore, we found that the concentration could influence the yield (Table 1, entries 9 and 11). Finally, the optimal yield (75%) of product **4a** was obtained when **3a** and **2a** (molar ratio 1:2) were stirred in DMSO in the presence of $AgNO_3$ (25 mol %) and $K_2S_2O_8$ (4.0 equiv) at rt for 16 h (Table 1, entry 11). Note that the reaction was insensitive to air, and the solvent could be used directly without pretreatment.

Table 1. Optimization of Reaction Conditions[a]



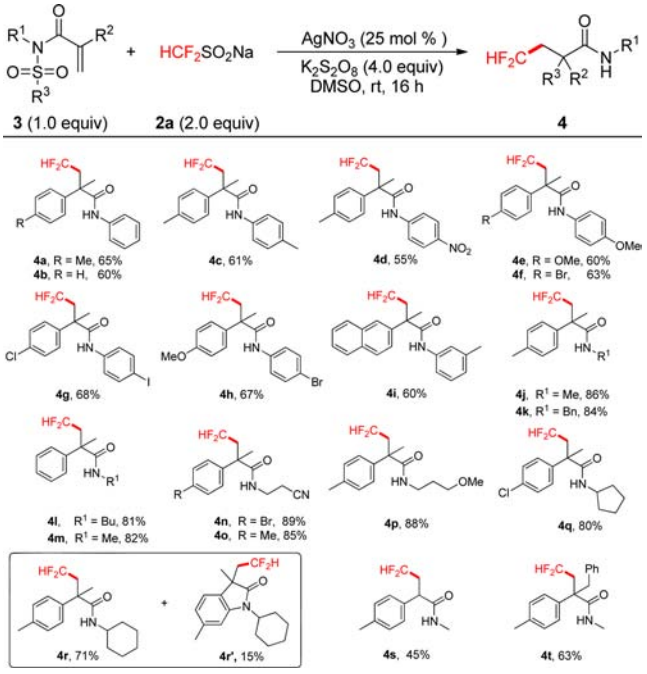
3a (1.0 equiv) 2a 4a

entry	2a (equiv)	solvent (mL)	cat. (mol %)	yield[b] (%)
1	2.0	DMF (1.5)	$AgNO_3$ (20)	trace
2	2.0	NMP (1.5)	$AgNO_3$ (20)	19
3	2.0	DMSO (1.5)	$AgNO_3$ (20)	62
4	2.0	CH_3CN (1.5)	$AgNO_3$ (20)	trace
5	2.0	DMSO (1.5)	AgOAc (20)	56
6	2.0	DMSO (1.5)	AgF (20)	54
7	2.0	DMSO (1.5)	Ag_2CO_3 (20)	48
8	2.0	DMSO (1.5)	$AgNO_3$ (15)	59
9	2.0	DMSO (1.5)	$AgNO_3$ (25)	69
10	1.6	DMSO (1.5)	$AgNO_3$ (25)	57
11	2.0	DMSO (2.0)	$AgNO_3$ (25)	75
12	2.0	DMSO (2.0)	none	trace

[a]Reaction conditions: **3a** (0.2 mmol), **2a**, cat., $K_2S_2O_8$ (0.8 mmol), and solvent were stirred at room temperature for 16 h. [b]Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as the internal standard.

By using the optimized reaction conditions (Table 1, entry 11), we examined the substrate scope of the present transformation (Scheme 2). First, we studied the influence of substituent R^1 at the N atom. The desired products **4a−i** could be obtained in moderate yields when R^1 was an aryl group. The introduction of electron-donating or -withdrawing groups at the aryl group had little influence on the yields. The nitro group (**4d**), methoxy group (**4e**), and halogen substituents (such as bromine (**4h**) and iodine (**4g**)), are well tolerated in the reaction. It is surprising that, when R^1 = alkyl groups (methyl, butyl, cyanoethyl, benzyl, and cyclopentyl groups), the reaction still gave α-aryl-β-difluoromethyl amides **4j−q**, and no cyclized products (difluoromethylated oxindoles) were formed; this is significantly different from Nevado's trifluoromethylation reactions using similar substrates.[15a] Interestingly, when R^1 = cyclohexyl group, both noncyclized product **4r** and cyclized product **4r′** were obtained in 71% and 15% yields, respectively. Moreover, we evaluated the influence of R^2 in the reaction and found that the yield decreased (45% for **4s**) when R^2 was changed from an alkyl group to H atom. When R^2 = benzyl group, the product **4t** (confirmed by single-crystal X-ray diffraction analysis, see the Supporting Information)[17] was obtained in 63% yield. Finally, we found that the substituent on the aryl group R^3 does not have a remarkable effect on the chemical outcome of the reaction; the reactions with methoxy-substituted substrate **3e** and brominated **3f** provided **4e** and **4f** in 60% and 63% yields, respectively.

Scheme 2. Difluoromethylation of Conjugated Arylsulfonyl Amides 3 with Reagent 2a[a,b]



3 (1.0 equiv) 2a (2.0 equiv) 4

[a]The reaction condtions were as follows: a mixture of **2a** (1.2 mmol), **3** (0.6 mmol), $AgNO_3$ (0.15 mmol), $K_2S_2O_8$ (2.4 mmol), and DMSO (6.0 mL) was stirred at room temperature for 16 h. [b]Isolated yield.

Encouraged by the aforementioned results, we further examined this fluoroalkylative aryl migration reaction with reagent **2b**. After a quick scan of the reaction conditions (see Tables S8−S11, Supporting Information), we found that the NMP/water cosolvent system was the best for the reaction. The optimal yield (60%) of product **5a** was obtained when **3a** and **2b** (molar ratio 1:2) were stirred in NMP/H_2O (7.5/1 v/v) in the presence of $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (4.0 equiv) at rt for 16 h. With the optimized reaction conditions as standard, we investigated the substrate scope of this difluoro(phenyl)-

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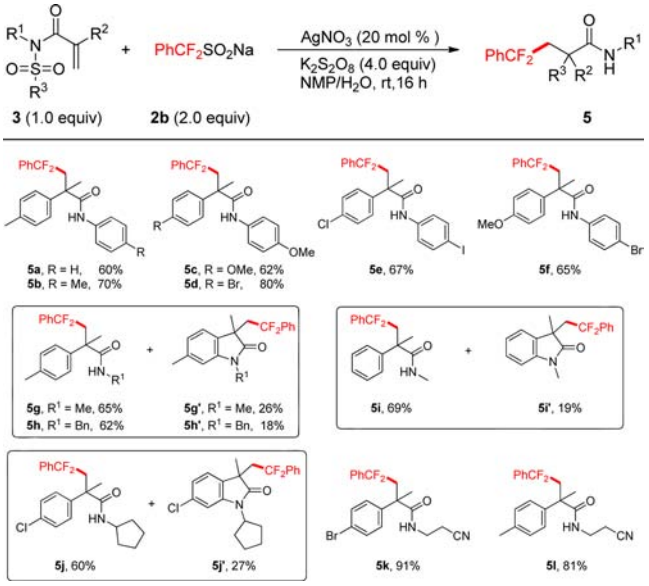
Scheme 3. Difluoro(phenyl)methylation of Conjugated Arylsulfonyl Amides 3 with Reagent 2b[a,b]

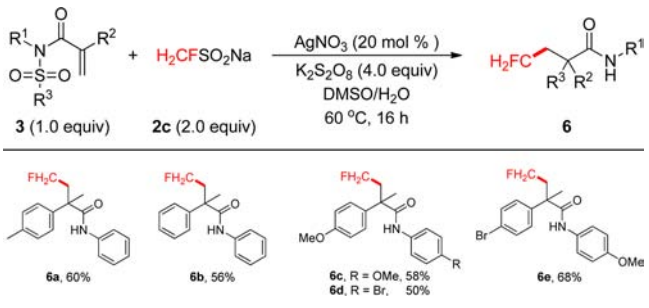


[a]The reaction condtions were as follows: **2b** (1.2 mmol), **3** (0.6 mmol), $AgNO_3$ (0.12 mmol), $K_2S_2O_8$ (2.4 mmol), NMP (4.5 mL), and H_2O (0.6 mL) were stirred at room temperature for 16 h. [b]Isolated yield.

methylation−aryl migration reaction (see Scheme 3). The desired products **5a−f** could be obtained in high yields when R^1 = aryl groups. When R^1 was an alkyl group, both noncyclized and cyclized products were formed in high total yields, with the cyclized product being the minor one (for **5g−j**). However, when R^1 was a cyanoethyl group, the reaction gave the noncyclized product (**5k** or **5l**) selectively in high yield.

Thereafter, we applied H_2CFSO_2Na (**2c**) in the reaction. We found that **2c** is less reactive than **2a** and **2b** in generating fluoroalkyl radicals. However, after optimization of the reaction conditions (see Tables S12−S17, Supporting Information), the optimal yield (60%) of product **6a** was obtained when **3a** and **2c** (molar ratio 1:2) were stirred in DMSO/H_2O (40:1 v/v) in the presence of $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (4.0 equiv) at 60 °C for 16 h. As is shown in Scheme 4, under the optimized conditions, the products **6a−e** could be obtained in moderate yields when R^1 = aryl groups. However, the yields of the desired

Scheme 4. Monofluoromethylation of Conjugated Arylsulfonyl Amides 3 with Reagent 2c[a,b]



[a]The reaction conditions were as follows: **2c** (1.2 mmol), **3** (0.6 mmol), $AgNO_3$ (0.12 mmol), $K_2S_2O_8$ (2.4 mmol), DMSO (21.0 mL), and H_2O (0.525 mL) were stirred at 60 °C for 16 h. [b]Isolated yield.

products were very low when R^1 = alkyl groups, probably due to the slow generation of CH_2F radical and the decomposition of the substrates at 60 °C.

To compare the reactivity of these different sodium sulfinates, the following competition experiments were carried out. First, when substrate **3a** and a mixture of three reagents **2a−c** were subjected to conditions A (the optimized reaction conditions of **2a** reacting with **3a**), the product **5a** was obtained in 64% yield, and only trace amounts of **4a** were observed. A similar result was obtained under conditions B (the optimized reaction conditions of **2b** reacting with **3a**). In addition, when the reaction was carried out under conditions C (the optimized reaction conditions of **2c** reacting with **3a**), the product **5a** was produced in only 8% yield (Figure 1A). These results show that the reactivity of **2b** is higher

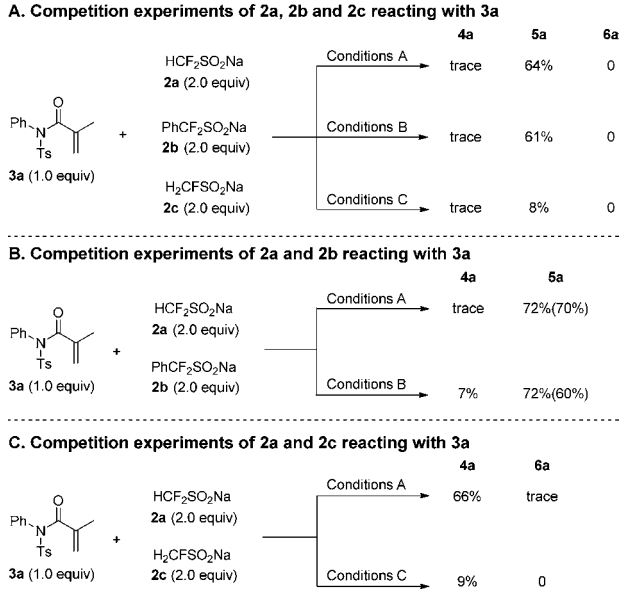


Figure 1. Competition experiments (A−C) on the reactivity of sodium sulfinate salts. Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. Isolated yields are given in parentheses. Conditions A: **3a** (0.2 mmol), $AgNO_3$ (0.05 mmol), $K_2S_2O_8$ (0.8 mmol), DMSO (2.0 mL), rt, 16 h. Conditions B: **3a** (0.2 mmol), $AgNO_3$ (0.04 mmol), $K_2S_2O_8$ (0.8 mmol), NMP (1.5 mL), H_2O (0.2 mL), rt; 16 h. Conditions C: **3a** (0.2 mmol), $AgNO_3$ (0.04 mmol), $K_2S_2O_8$ (0.8 mmol), DMSO (7.0 mL), H_2O (0.175 mL), 60 °C, 16 h.

than **2a** and **2c** in the reaction between **3a** and **2**. Moreover, the results also indicate that conditions C is not suitable for **2a** and **2b** in this reaction, and the presence of **2a** and **2b** could restrain the reaction between **3a** and **2c** under conditions C. Second, when **3a**, **2a** and **2b** were subjected to conditions A and B, the product **5a** was gained in high yield in both cases,[18] but the yields of **4a** were low (Figure 1B). These results once again indicate that the reactivity of **2b** is higher than **2a** regardless of conditions A or B. Finally, when **3a**, **2a**, and **2c** were subjected to conditions A and C, product **4a** was obtained in 66% and 9% yields, respectively (Figure 1C), and only a trace amount of **6a** was observed under conditions A. This result suggests that **2a** is more reactive than **2c** in our model reaction, and the presence of **2a** restrains the reaction between **3a** and **2c**. In combination with the aforementioned results, we could conclude that the reactivity of these sodium sulfinates in their reactions with **3a** decreases in the following order: **2b** > **2a** > **2c**.

Finally, in order to demonstrate the synthetic utility of our reagents in other fluoroalkylation reactions, we conducted the

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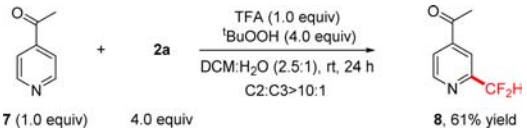

Figure 2. Difluoromethylation of 4-acetylpyridine with **2a**.

reaction between **2a** and 4-acetylpyridine (**7**) under Baran's difluoromethylation conditions[7b] and found that the C2-difluoromethylated product **8** was obtained in 61% yield, which was similar to the reported result (Figure 2).

In summary, a novel method for the preparation of sodium fluoroalkanesulfinates has been developed. This method provides a simple and efficient pathway for rapid large-scale preparation of sodium di- and monofluoromethanesulfinates. Furthermore, these sodium fluoroalkylsulfinates have proven to be good radical fluoroalkylation reagents that could react with conjugated *N*-arylsulfonylated amides to produce α-aryl-β-fluoroalkyl amides. This reaction has a wide range of scope of substrates. The reactivity order of these sodium fluoroalkanesulfinates in our reaction was also investigated. Investigations in the reaction mechanism and the application of these sodium fluoroalkanesulfinates in other reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and crystallographic data for **4t** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): The authors have filed a patent on the new preparative method for di- and monofluoromethanesulfinates.

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(17) CCDC 1044569 contains the supplementary crystallographic data for **4t**.

(18) It is interesting to note that under conditions A the reaction with **2b** in the presence of **2a** afforded **5a** in a higher yield than that conducted with **2b** only.

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